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June 28, 2004

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VIA HAND DELIVERY

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Dear Madam or Sir:

Ropes & Gray LLP hereby submits two (2) copies of Comments to Docket No. 2003D-0206.

Sincerely,

Gregory J. Glover

GWG:jyf
Enclosures

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Rockville, MD 20852

Re: Comments on Docket No. 2003D-0206; Draft Guidance for Industry on Exocrine Pancreatic Insufficiency Drug Products - Submitting New Drug Applications

Dear Madam or Sir:

Ropes & Gray LLP provides the following comments and recommendations on the Food and Drug Administration (FDA) "Draft Guidance for Industry on Exocrine Pancreatic Insufficiency Drug Products – Submitting New Drug Applications" (Draft Guidance) which was published for comment in the Federal Register on April 28, 2004. We support the FDA's efforts to provide safe and effective pancreatic enzyme products (PEPs) to patients with exocrine pancreatic insufficiency. The FDA's consistent application of prescription drug approval criteria to all products in this class will benefit patients and the healthcare professionals who treat them.

Along with the FDA, we recognize that PEPs have been marketed for many years, and that they may not meet today's standards for chemistry, manufacture and control (CMC) requirements. We endorse requiring modifications in the CMC of these products to enhance their ability to meet today's standards. However, such modifications may also alter these products significantly such that prior human experience is no longer adequate as an evaluation of their safety and efficacy. We believe it is important for the sponsors of these products to demonstrate that an improved product is comparable to the historical version of the same product, if the sponsor intends to depend on historical human safety and efficacy data for marketing approval.

Our detailed, line-specific comments are organized as follows:

- The line number(s) from the draft guidance are provided and underlined, followed by the exact wording from the FDA draft guidance in italics.
- Our comments/recommendations follow each such reference to the guidance.
- Our comments/recommendations are provided in the order in which the referenced sections appear in the draft guidance.

Lines 110-114: *For the starting material used in the manufacturing process, information on animal species, tissue types, and countries of origin should be provided. Animals used should have been raised with the intent for use as human food. When ruminant tissues are used, they should not be derived from cattle born, raised, or slaughtered in BSE (bovine spongiform encephalopathy) countries (see CFR 94.18).*

Manufacturers of PEPs should be required to justify their strategy for sourcing raw materials. Currently, monitoring of individual animals or herds for infectious diseases only follow animal husbandry practices. Because of the safety concern for potential infection by adventitious agents in patients receiving chronic treatment with PEPs, we believe that the identity and characterization of the source animals used for the manufacture of PEPs should be documented. We advocate better source documentation for infectious diseases and monitoring of infectious agents in source herds. These measures include documentation of animal origin, identification and movement since birth, maintenance of animal medical records, surveillance of herds, and documentation of feeds. Feed should not be permitted to contain any reprocessed animal products. Such documentation would facilitate the investigation of infections or other diseases that could potentially be attributed to infectious agents from the animal source for PEPs and whose detection in the drug substance/product is not feasible because validated assays are either not available or have inadequate sensitivity.

Lines 116-117: *The manufacturing (extraction and purification) process should be validated for its capability to remove and/or inactivate viral agents as recommended in ICH Q5A.*

We agree with the need to document the removal and/or inactivation of viral agents, as described in ICH Q5A. Patients with pancreatic insufficiency require chronic therapy and treatment in patients with cystic fibrosis is typically initiated shortly after birth. Both patient populations are compromised in their ability to clear infections.

The current source for PEPs is animals raised for human consumption and processed in slaughterhouses; in particular, hog (pig) pancreas is used to produce these products. Thus, in order to avoid infection with adventitious agents, it is important to include validation of the removal and/or inactivation of viral agents known to be pathogenic or endogenous to the source animals, including porcine endogenous retrovirus (PERV).

Lines 119-122: *The drug substance should be fully characterized (based on ICH Q6B) using appropriate chemical, physical, and biological testing. Batch-to-batch consistency with respect to chemical identity, biological activity of different classes of enzymes including specific activity, and purity level should be demonstrated.*

We agree that the PEP drug substance should be fully characterized and that such characterization should include chemical, physical and biological testing. For each class of enzyme, (e.g., lipase, amylase, and protease), the pattern of heterogeneity of individual enzymes should be determined.

This characterization should include identifying and quantifying the enzymes within a class that contribute to the potency of the product. Because biological activity varies among enzymes within a class, variability among specific enzymes within a class may impact clinical efficacy and/or patient safety.

Lines 132-134: *Specifications for the drug substance should include tests for identity, biological activity of different classes of enzymes, purity, and other relevant attributes. Appropriate acceptance factors (e.g., limits and ranges) should be established and justified.*

We agree that specifications for the drug substance should include tests for identity, biological activity, purity and other relevant characteristics. Specifications for each individual enzyme within a class that may impact safety or the desired clinical effect are also needed to ensure lot-to-lot consistency and reliable therapeutic effect. Establishing specifications only by class of enzyme is not adequate to ensure consistent performance across batches of drug substance.

Furthermore, we believe that applying these specifications will ensure a consistent ratio of enzymes within a brand across batches. Differences in enzyme ratios for different batches within a brand may result in inconsistent effectiveness over time for the same brand name and strength product. When a consistent ratio has been established, the drug substance should either be shown to be comparable to the product that has been marketed in the past, or, if the product has been significantly changed such that comparability cannot be established, clinical studies should be performed to support the label indication for the product to be marketed following approval.

Lines 138-140: *Specifications for the drug product should include tests for identity, biological activity of different classes of enzymes, degradants, dissolution, and other relevant attributes. Appropriate acceptance factors should be established and justified.*

As with drug substance, we agree that specifications for drug product must include tests for identity, purity, biological activity of different classes of enzymes, degradants, dissolution and other relevant attributes. In addition, specifications for each enzyme that contributes to the bioactivity of the product, not just the class of enzymes, must be established for the drug product, and each lot released must meet these specifications.

The draft guidance suggests that the many years of human usage of these products can be a basis for the demonstration of product safety. However, if these historical safety data are to be extrapolated to licensed products, then comparability between historical and NDA approved PEPs must be demonstrated. Failure to demonstrate comparability prevents the extrapolation of historical safety data, and adequate and well controlled clinical studies would be needed to demonstrate the safety and efficacy of PEPs approved under a NDA. Furthermore, FDA information accompanying the release of the draft Guidance indicates that data showed variations in manufacturing quality of the existing products. If products to be submitted for NDA approval include quality improvements relative to the historical product such that these

products are not comparable, the efficacy and safety of the NDA products should be demonstrated by adequate and well-controlled clinical studies.

Lines 154-155: *Primary stability studies should be performed with batches that are formulated to be released at 100 percent of the label-claimed potency.*

USP tests that measure bioactivity of lipase, protease and amylase are currently used to assess potency of these products. All assays have some inherent variability. Accordingly, specification ranges are set to include the relative change in a data point that one can expect for identical samples. The USP bioassays for lipase, protease and amylase demonstrate significant assay variability, and thus necessitate an acceptance specification that is set based upon the capabilities of the assay established during validation; a release specification of 80-120% is suggested. We recommend that this range be included within the guidance document to ensure consistent manufacturing limits such that overages, which may subject patients to highly variable protein concentrations over time, are not allowed as a means to overcome variable product quality or stability.

Line 169: *For novel dosage forms, an appropriate in vitro release test method should be developed.*

We agree that an appropriate in vitro release test method is necessary for novel dosage forms. However, we also believe that all dosage forms, whether or not novel, require an appropriate in vitro release test method as an aid in evaluating batch-to-batch consistency and monitoring manufacturing process changes over time. Product dissolution rates may significantly affect bioactivity, particularly in the case of enteric-coated products where controlled dissolution is a key component of the product's characteristics. As such, appropriate specifications for dissolution of each product should be set by the manufacturer, which must be met for product release.

Lines 178-182: *No toxicology studies are needed if excipients are classified as GRAS for oral administration. Safety should be established through toxicology studies of new excipient(s) of the drug product, which are not included under GRAS or not previously approved for the same route of administration, amount, or therapeutic use. For new excipients without previous clinical data, clinical trials of the drug product containing the new excipients should also be performed.*

We believe this statement could be interpreted to mean that a sponsor does not need to conduct toxicity studies for a modified product if the excipients for the product are GRAS. As discussed above, however, historical safety data is not relevant to modified products that cannot demonstrate comparability to the products for which historical safety data is available. Accordingly, for modified products that cannot demonstrate comparability, full safety information for the product should be required – including toxicity studies – regardless of the GRAS status of the excipients. This approach is consistent with the guidance provided in the

1996 FDA "Guidance Concerning Demonstration of Comparability of Human Biological Products including Therapeutic Biotechnology-derived Products." The need for toxicology studies appropriate for the chronic use of these products, as described in ICH guidance M3, and possibly human clinical studies depends upon the ability to demonstrate comparability and the potential for the differences in the product to affect safety and efficacy.

Lines 204-207: *The bioactivity and/or bioavailability of the active ingredients should be determined at the site of action (gastrointestinal tract). The lipase, amylase, and protease activities should be determined from aspirates from the stomach and duodenum. The data should be obtained under fasting conditions as well as after a standard meal stimulation.*

We recommend that, if a relevant clinical or surrogate endpoint demonstrates clinically meaningful evidence of efficacy with respect to an active ingredient, demonstration of bioactivity in the gastrointestinal tract should not be required for that active ingredient.

Lines 209-211: *The use of any inactive ingredient to prevent or minimize the hydrolysis of the enzymes in the stomach should be supported with in vitro and/or in vivo release data. An appropriate in vitro release test method should be developed.*

We recommend that, at a minimum, a dissolution test method with appropriate specifications must be established for each product dosage form and strength. As noted in the April 28, 2004 Federal Register notice (Docket # 2003N-0205), variations in release patterns for PEPs that may impact product efficacy (e.g., encapsulated enteric-coated products) have been reported. By establishing appropriate release tests, batch-to-batch conformance for a product will be better controlled. Also, as stated above, because of the variability demonstrated in USP bioassays for lipase, protease and amylase, we recommend inclusion of a release specification of 80-120% within the guidance document.

Lines 231-233: *With improvements in quality as outlined in the guidance, therapeutic performance may be better predicted from in vitro studies or from in situ measurements of PEP bioactivity in the small intestine.*

We agree that establishing a product with known and reproducible quality, potency, and purity should provide a more consistent clinical effect. However, with improvements in quality, the improved product may not have comparable efficacy and safety to the historical product. In vitro studies alone may not be adequate to predict therapeutic performance of the improved product. Therefore, in order to ensure comparable therapeutic performance, we recommend that human in situ measurements or clinical studies be required.

Lines 248-250: *At a minimum, because cystic fibrosis is primarily a pediatric disease, the efficacy studies in the NDA should include clinical studies in pediatric patients with cystic fibrosis.*

This language could be interpreted as suggesting that a sponsor could seek a label claim for cystic fibrosis based exclusively on studies of pediatric populations. Given the demographics of cystic fibrosis, such limited studies should not be sufficient to support a label claim for cystic fibrosis. Therefore, this language should be changed to state that a claim for cystic fibrosis will require studies of pediatric and adult populations.

Lines 254-256: *Although demonstrating a beneficial effect on clinical outcomes is desirable in clinical trials (e.g., weight gain or nutritional status), efficacy can also be demonstrated by showing a meaningful beneficial effect on appropriate pharmacodynamic measures such as steatorrhea.*

The currently marketed PEPs should be considered as 'combination drugs" as defined in 21 CFR 300.50 because they contain three classes of enzymes, lipase, protease and amylase, each of which has a different effect on digestion. Therefore, the contribution that each enzyme component makes to the claimed effects and the dosage (amount, frequency, duration) of each component that is safe and effective should be demonstrated in clinical studies in the patient population defined by the labeling of the drug.

Lines 281-284: *In an effort to minimize development of fibrosing colonopathy that has been assumed to be related to high doses of PEPs, the FDA, in conjunction with the Cystic Fibrosis Foundation (CFF), recommends a starting dose titration of 1500-2500 lipase units/kg/meal, not to exceed 6000 lipase units/kg/meal (Borowitz et al, 1995).*

We believe that the doses stated in this section are not correct. It is our understanding that in this reference (Borowitz et al 1995), the CFF recommends not exceeding a dose of 2,500 lipase units/kg/meal, rather than the 6,000 lipase units/kg/meal as stated in the draft FDA guidance.

The cause of fibrosing colonopathy is unknown. However, since this condition may be associated with an enzyme component, an inactive component or a combination of active and inactive components, if the amounts and/or ratios of enzymes are not comparable to the historical version of the same product, safety of the product should be established for marketing approval.

Lines 298-301: *As noted in the sections below, if a placebo is not used (such as in a comparison of two doses of a PEP, or in a comparison of one PEP with another (e.g., an active control)), differences between treatments should be demonstrated to help interpret results.*

This statement could be interpreted as suggesting that dose-response studies are not required if a placebo is used. We note, however, lines 235-237 which require dose-response studies. Accordingly, this language should be revised to make clear that this text does not eliminate the need for dose-response studies.

Lines 306-307: *The total numbers of patients in the study can be between 10 and 25, depending on study design.*

Given the variability in clinical efficacy that is expected in pancreatic insufficiency patients such as that reported by Stern *et al.*[1], we do not believe that 10-25 patients will generate statistically meaningful results for the primary endpoint(s). Please clarify whether FDA is willing to accept and approve NDAs for these products based on the statistical information that can be raised from 10-25 patients.

In addition, FDA should make clear whether it will consider the suggested studies of 10-25 patients to be adequate and well-controlled studies sufficient for the marketing approval of PEPs and other products intended to treatment of pancreatic insufficiency.

* * *

We appreciate the opportunity to submit these comments.

Sincerely,

Gregory J. Glover

GWG:jyf

[1] Stern RC, Eisenberg JD., Wegener JS, Ahrens R, Rock M, doPico G, and Orenstein DM. A comparison of the efficacy and tolerance of pancrelipase and placebo in the treatment of steatorrhea in cystic fibrosis patients with clinical exocrine pancreatic insufficiency. Am. J. Gastroenterol. 2000; 95:1932-1939.